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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/541,844	04/03/2000	Jacob S. Tou	SO-3181-00-US	4246

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EXAMINER	
WEBER, JON P	
ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 06/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/541,844	TOU ET AL.	
	Examiner	Art Unit	
	Jon P Weber, Ph.D.	1651	

-- The MAILING DATE of this communication appears n the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-68* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-68* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114.

Applicant's submission, response with amendments, filed on 07 April 2003 has been entered. Claims 22-68 have now been presented for examination.

Claim Rejections - 35 USC § 112

Claims 61-68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 61 recites "mobilized" which is vague and indefinite because the term does not appear to have been used or described in the instant disclosure. There are several common meanings for this term in biochemistry. It is not clear which of these various meanings is intended. It appears from the citation of the portion of the specification alleged to support this terminology, that it is intended that the enzyme is soluble as opposed to immobilized. If so, the claim should precisely say so.

Claim Rejections - 35 USC § 102

Claims 61-63 and 66-67 are rejected under 35 U.S.C. 102(e) as being anticipated by Blumberg et al. (US 5,763,215) and Blumberg et al. (EP 191,827).

Blumberg et al. (US 5,763,215) has been reconsidered and the original rejection under this statute reinstated. The teachings of Blumberg et al. (US 5,763,215) have been presented in the Office action of 28 August 2001.

It is argued that Blumberg et al. (US 5,763,215) teach away from the claimed invention because: 1) the recombinantly made hSOD used is not explicitly recited, just that the N-terminal Ala is not acetylated, 2) AAP inefficiently removes Ala from its terminus, 0.53 moles of an expected 10.17 moles, and the authors refer to non-removal of Ala, 3) the ability to remove multiple amino acids is speculative, based on several statements.

The instant claims only require that AAP remove Ala from the N-terminus of proteins, especially proteins that are recombinantly made. No degree of efficiency is required! It is clear that Blumberg et al. (US 5,763,215) do teach that Ala can be removed, albeit with the example hSOD provided, only 5% was removed. Further, Blumberg (US 5,763,215) carry out the reaction at pH 9.5 which is about midpoint in the claimed range of pH 7-11. That is, the same enzyme is used under the same conditions as instantly claimed. Even if no results had been shown, a person of ordinary skill in the art would reasonably expect that the same cleavage pattern should result as instantly claimed unless the differences are due to undisclosed effects (*In re Sussman*, 141 F. 2d 267, 60 U.S.P.Q. 538 (CCPA 1944) "since the steps are the same, the results must inherently be the same unless they are due to conditions not recited in the claims"). In this particular case, the claimed invention employs the same process steps but the products are alleged to be

different. In view of the different results obtained in different laboratories with the same enzyme and under the same conditions, there are only two possibilities to explain the differences: 1) somebody goofed in one or both of the labs (not too likely), or 2) there is an inherent difference in the ability of AAP to act on large polypeptides that varies from polypeptide to polypeptide. In support of this latter inherent effect, the following references, Prescott et al. (1971), Wagner et al. (1972), Wilkes et al. (1973) and Prescott et al. (1975), are provided to show that it is old and well known in the art that the ability of AAP to act on peptides and polypeptides is not only processive (contrary to argument 3 above), but does in fact vary from sequence to sequence. There is influence from adjacent residues as well as N-terminal accessibility issues with a full size polypeptide.

Claims 61-64 and 66-67 are rejected under 35 U.S.C. 102(e) as being anticipated by Pederson et al. (US 5,783,413).

Pederson et al. (US 5,783,413) has been reconsidered and the original rejection under this statute reinstated. The teachings of Pederson et al. (US 5,783,413) have been presented in the Office action of 28 August 2001.

It is argued that Pederson et al. (US 5,783,413) in example 9 does not really use AAP. It is asserted that AAP is a typographical error in this example and the enzyme used is APP mentioned twice in this example compared to once for AAP. It is urged that the materials and methods do not recite a method for making AAP.

Throughout Pederson et al. (US 5,783,413), the discussion focuses on AAP, not APP. For example at Column 3, lines 1-12,

> Another example of the use of an exopeptidase in connection with the removal of a terminal extension from a protein with a natural stop point is the use of the enzyme

aeromonas aminopeptidase (AAP), which removes single amino acids from the N-terminal of a protein or polypeptide, cf. EP 489 711 and EP 191 827 disclosing removal of N-terminal residues by means of an aminopeptidase, e.g. AAP. Under appropriate conditions, amino acid removal will commence and continue unless or until (1) the amino group of the N-terminal is blocked, (2) the site of removal is on the N-terminal side of proline, or (3) the N-terminal amino acid is glutamic acid or aspartic acid.

At column 3, lines 27-45,

DAP I and AAP may thus have some usefulness in the production of a desired recombinant protein from a precursor protein by constructing such precursor protein to contain a removable N-terminal extension, i.e. an extension which does not contain any of the above-mentioned stop points. Treatment of the precursor protein with either of the two enzymes may result in removal of the N-terminal extension.

This process, however, may be severely limited in its application, as dipeptide or amino acid removal by DAP I or AAP, respectively, will continue sequentially and unhindered until one of the aforedescribed termination sequences (stop point) is reached. Thus, the aminopeptidase approach should find limited use, being applicable generally only in those instances in which the N-terminal portion of the desired protein product is itself a DAP I or AAP stop point.

At column 4, lines 48-52,

The choice of aminopeptidase(s) depends on the amino acid sequence in A or vice versa. A is i.e. constructed according to the used aminopeptidase(s). The aminopeptidases are chosen according to their suitablity in connection with the specifically constructed extended protein.

At column 5 line 65 to column 6, line 6,

Further, it has surprisingly been found that using AAP together with a surplus of GCT in an enzymatic reaction containing the N-terminal extended protein product, GCT will cyclizise the glutamine residue to a pyroglutamine residue, as soon as AAP has removed all the amino acids before the glutamine residue. This cyclization reaction will thus result in a blocked N-terminal immediately before the desired protein product, and the reaction catalyzed by the aminopeptidase(s) will not proceed any further.

Accordingly there is no clear basis for the assertion that APP was the intended enzyme in example 9. It seems more likely in view of especially this last quote (the conditions of example 9) that the intended enzyme was AAP and that APP was the typographical error. A review of the file wrapper reveals that the typographical error was not introduced by the printer.

The quotes above also indicate the processive nature of AAP and refers to the Blumberg patent. AAP is so well known and its method of preparation is so well known that it was not necessary to provide a method of making (see the evidence references noted above.)

Hence, contrary to the assertion in the response, Pederson et al. (US 5,783,413) does teach treating tag-extended TNF produced recombinantly in bacteria with AAP to remove the tag. The tag is removed completely up to the Gln residue (see the last quote). Hence, at one point of the sequence of tag removal, the N-terminus was in fact Ala.

Applicant's arguments filed 07 April 2003 have been fully considered but they are not persuasive. The rejections under 35 U.S.C. 102 are adhered to for the reasons of record and the additional reasons above.

Claim Rejections - 35 USC § 103

Claims 22-68 are rejected under 35 U.S.C. 103(a) as being unpatentable over Blumberg et al. (US 5,763,215) and Pederson et al. (US 5,783,413) in view of Prescott et al. (1975) and Prescott (1966).

It is argued that the references do not teach immobilized AAP and the other arguments recited above.

The teachings of Blumberg et al. (US 5,763,215) and Pederson et al. (US 5,783,413) have been presented earlier. Blumberg et al. (US 5,763,215) and Pederson et al. (US 5,783,413) lack exemplifying the removal of N-terminal Ala with immobilized AAP, and do not exemplify every one of the proteins specifically claimed.

Prescott et al. (1975) discloses that AAP is processive and demonstrates that the effectiveness of the N-terminal cleavage reaction depends 1) on the nature of the adjacent residue, and 2) the specific nature of the polypeptide.

Prescott (1966) discloses that AAP cleaves di- and tripeptides with Ala on the N-terminus (Table 3),

Blumberg et al. (US 5,763,215) explicitly suggest that AAP may be immobilized at column 2, lines 62-65,

> In specific embodiments an aminopeptidase which is insoluble in water may be used. The aminopeptidase may also be used while it is bound to a solid support, or may be removed at the end of the reaction by use of an affinity resin.

Both Blumberg et al. (US 5,763,215) and Pederson et al. (US 5,783,413) specifically indicate that the method is of broad applicability to proteins because of the processive nature of AAP as shown by Prescott et al. (1975). Hence, the selection of a particular protein, naturally occurring or non-naturally occurring, is an arbitrary matter of experimental design choice absent evidence of unexpected results. While not removing an Ala from the N-terminus (Met is removed) hGH (one of the instantly claimed proteins) was one of the proteins exemplified by Blumberg. Clearly, the Ala starts in the N-terminal region in example 9 of Pederson. The ability to cleave Ala from any given polypeptide is somewhat dependent on the sequence and accessibility of the N-terminus according to Prescott et al. (1975). Prescott et al. (1966), especially, establishes that Ala in the N-terminus is cleaved by AAP.

Applicant's arguments filed 07 April 2003 have been fully considered but they are not persuasive. The rejection under 35 U.S.C. 103 is adhered to for the reasons of record and the additional reasons above.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 703-308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Jon P Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
June 12, 2003